A. Provisional Double Patenting Rejection

The Examiner has provisionally rejected Claims 1-4 for obviousness double patenting based on Claims 13-17 of copending application Serial No. 08/055,519. Applicants will respond to this rejection as prosecution in both cases proceeds.

B. Section 112 Rejections

The Examiner has objected to the specification and rejected Claims 1-4 under section 112 for a variety of reasons. Applicants respectfully traverse these rejections.

1. Use Of "Treatment"

First, it is the Examiner's position that the specification fails to describe what constitutes "treatment" and that there is no common and well-known meaning for this term. To the contrary, "treat" and "treatment" are well-known terms having established meanings. In particular, "to treat" means "to seek cure or relief of a disease." See Webster's Third New International Dictionary, page 2435 (1961) (copy being submitted herewith). Accordingly, a definition of "treat" or "treatment" in the specification is not necessary, and this rejection should be withdrawn.

2. Breadth Of The Claims

Second, it is the Examiner's position that the claims are too broad in the recitation of any cancer. Applicants disagree. They have provided examples of the effective treatment of the following diverse cancers having very different etiologies: fibrosarcoma, synovial sarcoma, colon carcinoma, breast carcinoma, prostate carcinoma, lung large cell carcinoma, cervical carcinoma, neuroblastoma,

glioblastoma, and melanoma. See Examples 1-3 and 5. Clearly, Applicants' data show that NDV can be used to treat cancer in general.

The Examiner states that "leukemia cells appear to be unresponsive to NDV (based on the art), and metastasis has not been addressed." The Examiner has not cited a source for the statement about leukemia cells, which she must do, but it is believed to be based on Reichard et al. However, the result reported in Reichard et al. is based on the in vitro testing of only one leukemic cell line. See the accompanying Declaration of Dr. Robert M. Lorence, paragraph 2. There are several different types of leukemia, and the results with one cell line in an in vitro test do not support the conclusion that NDV does not work against leukemia. Moreover, it is not the function of the claims to exclude all possible inoperative embodiments. Atlas Powder Co. v. E.I. du Pont & Co., 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409 (Fed. Cir. 1984).

The Examiner is correct that Applicants have not provided a specific example of the use of NDV to treat metastasis. However, in the experiments described in Example 2, NDV was administered sytemically at a site remote from established tumors and was able to cause regression of the tumors. In addition, Dr. Lorence's Declaration, paragraph 3, provides another example of the systemic administration of NDV to treat established tumors. Complete regression of the tumors was achieved. In addition, tissue samples from the test animals were examined, and NDV was found to be present in tumor tissue but not in normal tissue. The combined results show that the NDV was able to reach, replicate in, and destroy tumor tissue when injected systemically. For the treatment of metastasis, NDV would

also be administered sytemically at a site remote from the tumor. Thus, Example 2 and the additional example in Dr. Lorence's Declaration provide evidence that NDV can be expected to reach and destroy metastases. See Lorence Declaration, paragraph 3.

Finally, the Examiner states that: "The results achieved in [the] instant examples are not predictive of the effect of NDV on all cancers as claimed." This statement directly contradicts the Examiner's obviousness position. Obviousness requires a reasonable expectation of success, and something cannot be both unpredictable and expected.

For all of the foregoing reasons, this rejection should be withdrawn.

3. Use Of NDV With Another Agent

Third, it is the Examiner's position that the claims directed to the use of NDV in combination with other anti-cancer agents are not enabled. By the above amendments, the claims have been limited to chemotherapeutic compounds as the anti-cancer agent. Applicants have provided substantial general disclosure of how to use NDV and these chemotherapeutic compounds in combination (see page 14, lines 3-25 and page 15, line 21 through page 16, line 31 of the specification). In addition, an example of the use of NDV in combination with one such chemotherapeutic compound (retinoic acid) in vitro is described in Reichard et al., J. Ped. Surg., 28, 1221-26 (1993) (already of record). This article reports that retinoic acid[1] substantially enhances the killing of tumor cells by NDV.

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[1] For more information about retinoic acids, see Claxton et al., J. Nat'l Cancer Inst., 84, 1306-1307 (1992) and Adamson et al., J. Nat'l Cancer Inst., 84, 1332-1335 (1992) (copies being submitted herewith).

From the foregoing, it can be seen that the use of NDV in combination with chemotherapeutic compounds is clearly enabled, and this rejection should be withdrawn.

4. Recitation Of Process Steps

Fourth, the Examiner has rejected the claims as indefinite for failing to recite proper process steps. The Examiner relies on Ex parte Erlich in making this rejection.

The claims at issue in Erlich were Claims 6 and 7.[2] With respect to these claims, the Board of Appeals stated:

> We agree with the examiner that appellants' reliance upon *Bull* is misplaced because the claims under consideration in the prior appeal did recited active, positive steps such as "bringing together...," "providing," and "maintaining." Here, claims 6 and 7 merely recite a use without any active, positive steps delimiting how this use is actually practiced. While we agree with appellants that the claims need not recite all of the operating details, we do find that a method claim should at least recite a positive, active step(s) . . . .

Ex parte Erlich, 3 U.S.P.Q.2d 1011, 1017 (PTO Bd. App. Int. 1986).

"Administering" is a positive, active step such as "providing" or "maintaining." Thus, the present claims recite a proper process step as required by Erlich.

It is also the Examiner's position that Applicants should specify in the claims where and how and in what amount the virus is administered, whether the virus is live or attenuated, and the amount of the chemotherapeutic compound. Erlich clearly states that such operating details are not required.

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[2] The text of Claims 6 and 7 is set forth below:

6. A process for using monoclonal antibodies of Claim 4 to isolate and purify human fibroblast interferon.

7. A process for using monoclonal antibodies of Claim 4 to identify human fibroblast interferon.

Moreover, Applicants have specified the amount of virus and chemotherapeutic compound in the claims ("an effective amount"). What constitutes an effective amount of virus and chemotherapeutic compound and where and how the virus and chemotherapeutic compound are to be administered are disclosed in great detail in the specification (see page 13, line 5 through page 14, line 13 and page 15, line 21 through page 16, line 31). Since "administering" and "effective amount" are defined in the specification, the claims are clear and definite without including all of the details in the claims.

Finally, the Examiner states: "It is additionally noted that based on the art, the amount of virus to be administered may vary significantly, and toxicity of virus based on solubility parameters appears to be an important consideration." The Examiner has not cited a source for this information, which she must do, making it very difficult for Applicants to respond. Applicants have explained in the present application what constitutes an effective amount of virus and that this amount may vary (see above and portions of the application cited there). In addition, Applicants have found that the toxicity of NDV preparations, if any, is due to impurities, not to NDV. Any toxicity problems can be avoided by using the method of isolating NDV described in the present application (see the discussion of Reichard et al. below).

For all of the foregoing reasons, this rejection should be withdrawn.

C. Section 102 Rejections

1. Cassel et al.

The Examiner has rejected Claims 1-4 as anticipated by Cassel et al. This rejection is respectfully traversed.

Cassel et al. discloses the administration of a viral oncolysate to melanoma patients to stimulate the immune responses of the patients to their cancers. The oncolysate was prepared as described in Cassel et al., Cancer, 40, 672-79 (1977) (hereinafter "Cancer article"; already of record) using NDV to infect and lyse melanoma cells in vitro.

The oncolysate administered to patients contained live NDV, as well as lysed melanoma cells, but the NDV was not administered in an effective amount for treating melanoma. See Lorence Declaration, paragraph 4. In particular, Dr. Lorence's calculations show that Cassel et al. used 10,000 times less NDV per kilogram than the amount used in the present application to locally treat tumors and 1,000,000 times less NDV per kilogram than the amount used in the present application to systemically treat tumors.

Further, the Cassel et al. oncolysate was injected subcutaneously at a site remote from the tumor (see page 857, second full paragraph, and Table 1 of Cassel et al.).[3] It is unlikely that the virus was able to reach the tumor in vivo since it was not administered directly to the tumor,

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[3] The oncolysate was injected over the anterior thighs of the patients. One of the patients had the primary lesion on the thigh (patient 9; see Table 1, page 858 of Cassel et al.), but there is no indication that the oncolysate was injected near the site of this lesion. Indeed, it is doubtful that any apparent primary tumor remained in this patient since Table 1 indicates that this primary thigh lesion had been examined for precise tumor thickness, implying that surgical removal and histological examination had been performed.

nor was it given at an effective dose to reach distant tumor tissue. Indeed, the amount of NDV used by Cassel et al. has been found ineffective by Dr. Lorence for treating cancer when administered systemically at a site remote from the tumor. See Lorence Declaration, paragraph 4.

Also, only the treatment of melanoma (not a carcinoma or sarcoma) is taught, and the use of NDV in combination with a chemotherapeutic compound is not disclosed.

For all of the foregoing reasons, the claimed methods are not anticipated.

2. Murray et al.

The Examiner has rejected Claims 1-4 as anticipated by Murray et al. This rejection is respectfully traversed.

Murray et al. discloses the administration of a viral oncolysate to melanoma patients to stimulate the immune responses of the patients to their cancers. The viral oncolysate used by Murray et al. is the same as that used in Cassel et al. and it is was used in the same manner as in Cassel et al. Accordingly, Murray et al. does not anticipate the claimed methods for the same reasons as discussed above for Cassel et al.

3. Bohle et al.

The Examiner has rejected Claims 1-4 as anticipated by Bohle et al. This rejection is respectfully traversed.

Bohle et al. describes the intracutaneous administration of an autologous tumor cell vaccine to patients with colorectal carcinoma to stimulate the immune

responses of the patients to their cancers. The vaccine was prepared by infecting the tumor cells with a nonlytic strain of NDV. The vaccine contained live NDV, but the NDV was not administered in an effective amount for treating the patients' cancers. See Lorence Declaration, paragraph 4. In particular, Dr. Lorence's calculations show that Bohle et al. used 1,000 times less NDV per kilogram than the amount used in the present application to locally treat tumors and 100,000 times less NDV per kilogram than the amount used in the present application to systemically treat tumors.

Further, the Bohle et al. preparation was injected intracutaneously at a site remote from the tumor (see page 1518, line 4 of the second column, and Table 1 of Bohle et al.). It is unlikely that the virus was able to reach the tumor in vivo since it was not administered directly to the tumor tissue, nor given at an effective dose to reach distant tumor tissue. Indeed, the amount of NDV used by Bohle et al. has been found ineffective by Dr. Lorence for treating cancer when administered systemically at a site remote from the tumor. See Lorence Declaration, paragraph 4.

Also, only the treatment of carcinoma is taught, and the use of NDV in combination with a chemotherapeutic compound is not disclosed.

For all of the foregoing reasons, the claimed methods are not anticipated.

D. Section 103 Rejection

The Examiner has rejected Claims 1-12 as obvious over Reichard et al. This rejection is respectfully traversed.

The Examiner states: "It is noted that although

Reichard et al appears in the Journal of Surgical Research in May of 1992, the paper was presented at the Annual Meeting of the Association for Academic Surgery in November of 1991." However, the article and the presentation merely described the work of Drs. Reichard and Lorence, the inventors of the present application. See Lorence Declaration, paragraph 5. Therefore, neither the article, nor the presentation, is prior art to the present application. See In re Katz, 687 F.2d 450, 454, 215 U.S.P.Q. 14 (CCPA 1982) ("Disclosure to the public of one's own work constitutes a bar to the grant of a patent . . . only when the disclosure . . . creates a one-year time bar, frequently termed a 'statutory bar,' to the application under § 102(b).").

Moreover, Reichard et al. would not have made the presently claimed invention obvious. The claimed invention comprises the use of NDV for the treatment of cancer in a mammal already having cancer. Reichard et al. does not teach the treatment of such established cancers. Reichard et al. merely teaches the simultaneous injection of tumor cells and NDV (see paragraph bridging pages 449-450 of Reichard et al.). The simultaneous injection of tumor cells and NDV is not predictive of results against established cancers, especially of the complete regression of established tumors obtained by Applicants (see Examples 1-3 and 5 of the present application). Indeed, Reichard et al. specifically states that further work will be necessary before established cancers can be treated (see the last sentence of Reichard et al.).

In addition, the dose used in the present application to treat established cancers is at least ten times greater than that used in Reichard et al. for the

simultaneous administration of tumor cells and virus (at least 1 x 10^7 PFU per mouse per injection[4] versus 1 x 10^6 PFU per mouse per injection in Reichard et al.). The use of these much higher doses is not taught or suggested by Reichard et al. Indeed, the use of these higher doses is contrary to the teachings Reichard et al. which suggests that only a small number of NDV will be necessary for systemic treatment of tumors (see lines 2-4 from the bottom of the second column on page 452 of Reichard et al.).

In addition, Applicants found that using the virus purification procedure set forth in Reichard et al. produced an NDV preparation which was toxic when the virus was administered in the large doses necessary to treat established cancers. A different purification procedure had to be developed to overcome this toxicity problem to allow the administration of doses of NDV effective to treat established cancers.[5] The toxicity problem and how to overcome it are not taught or suggested by Reichard et al. since Reichard et al. does not contemplate the use of such large doses of NDV.

Claim 20 is directed to the systemic treatment of established cancers. There is nothing in Reichard et al. that teaches or suggests the successful systemic treatment of established cancers. In particular, as discussed above,

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[4] This dose of 1 x 10^7 PFU per mouse is approximately 4 x 10^8 PFU per kilogram body weight, assuming a 25 gram mouse. This is the dose for intralesional administration of NDV to treat established cancers. For systemic administration, a dose of at least 4 x 10^9 PFU per kg of body weight is required. See Example 2 of the present application. Also, see generally page 13, lines 13-35 and Examples 1-3 and 5 of the present application.

[5] This is the purification procedure set forth in Example 1 of the present application. The removal of contaminating red cell debris was found to be of particular importance to obtaining a safe NDV preparation.

it has been found that much higher doses of NDV than the dose used in Reichard et al. are necessary for the successful systemic treatment of established cancers (10^8 to 10^9 PFU per mouse per injection versus 10^6 PFU per mouse per injection for Reichard et al.; see page 13, lines 19-22 and Example 2 of the present application), and these higher doses of NDV are not taught or suggested by Reichard et al. In addition, the simultaneous administration of tumor cells and virus at the same site as was done in Reichard et al. is not predictive of whether systemic treatment will be successful.

Claims 25 and 26 are directed to the use of NDV in combination with a chemotherapeutic compound to treat cancer. Reichard et al. does not teach or suggest the use of NDV in combination with a chemotherapeutic compound.

Claim 18 is directed to the treatment of certain specified cancers. Reichard et al. does not teach or suggest the treatment of established cancers of these types.

Claims 23 and 24 are directed to the use of mesogenic strains of NDV such as NDV strain M (MK107). These are less virulent strains than the 73T strain used in Reichard et al. (see Example 3 of the present application and Hanson et al., Science, 122, 156-57 (1955)(copy being submitted herewith). There is nothing in Reichard et al. to teach or suggest that a less virulent strain would be effective in treating cancer, especially since Reichard et al. teaches that the anti-cancer activity of NDV is due to its ability to kill tumor cells (see, e.g., the abstract of Reichard et al.).

The claimed invention also comprises the use of NDV for the detection of cancer. Reichard et al. does not teach or suggest using NDV in this manner.

Finally, the Examiner's attention is drawn to Reichard et al., "Newcastle Disease Virus Selectively Kills Human Tumor Cells," The Association For Academic Surgery Twenty-Fifth Annual Meeting, page 152 (November 20-23 1991) (already of record). This is the abstract for the November 1991 meeting referred to in the cited Reichard et al. article. The abstract describes some of the same work as does the cited Reichard et al. article, but it contains considerably less information and data than the cited article. This abstract is, therefore, distinguishable from the claimed invention for the same reasons given above for the cited Reichard et al. article.

For all of the foregoing reasons, this rejection should be withdrawn.

CONCLUSION

The pending claims are believed to be in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

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